REMARKS

Applicant's attorney wishes to thank the Examiner for discussing the above-identified patent application during a telephone interview on Monday, December 29, 2003. Applicant's summary of the interview is as follows.

The Examiner suggested alternative wording for some of the claims. The Examiner also discussed certain case law and how the case law applied in the present case. Also discussed were certain possible arguments for applicant's use in the present case. The Examiner also indicated that he would consider allowing all or some of the claims upon first action after the filing of an RCE in the above-identified application.

Claims 1 to 64 have been canceled, without prejudice, and claims 65 to 71 have been added. The new claims are fully supported by the present specification and include no new matter.

The Examiner has restricted the scope of the present invention to one SEQ ID NO. Applicant has previously traversed this requirement.

Applicant submits that if the claims which relate to SEQ ID NO 2 are allowed, the Examiner should consider allowing claims 66, 69 and 70 which include certain other SEQ ID NOs. This is because, for example, the SEQ ID NOs included in claims 66 and 69 each relate to specific sequences which are encompassed by SEQ ID NO 2. That is, the SEQ ID NOs listed in claims 66 and 69 are consistent with, and included in SEQ ID NO 2. In addition, the SEQ ID NOs which are included in claim 70 are each closely related to SEQ ID NO 2. For example, all of the SEQ ID NOs included in claim 70 are seven amino acids in length. Further, all of the SEQ ID NOs in claim 70 have two hydrophobic amino acids at positions numbers 6 and 7, each being selected from L or I or, as in one case (SEQ ID NO 15), M. Further, all of the SEQ ID NOs have an acidic amino acid at position number 2 which

is selected from E or D or, as in one case (SEQ ID NO 17), Q. Therefore, applicant submits that if the claims relating to SEQ ID NO 2 are allowed, then claims 66, 69 and 70 should also be allowed.

The Examiner rejects the claims under 35 USC 112, first paragraph, as failing to satisfy the written description requirement. Citing Fiers v. Revel 25 USPQ2d 1601, 1606 (Fed. Cir 1993), the Examiner states that what is required is a description of the DNA itself. The Examiner also cites Univ. California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) stating that applicants were not reasonably in possession of the claimed genus of modified botulinum toxin serotype A proteins at the time of filing.

Applicant traverses the rejection.

Applicant submits that the sequence of botulinum toxin type A was well known in the art at the time of filing of the above-identifed application. See, for example, Binz et al J. Biol. Chem. v 265, p. 9153-9158 (copy included) and Minton, *Clostridial Neurotoxins the Molecular Pathogenesis of Tetanus and Botulism* Springer-Verlag: Berlin; 1995: 161-194 (copy included) each of which fully discloses an amino acid sequence of botulinum toxin type A. Further, all botulinum type A toxins are not only produced by the same genus and species of organism, but are produced by the same strain of organism; i.e., *Clostridium botulinum* serotype A. Moreover, it is well known in the fields of microbiology and molecular biology that proteins, such as toxins, produced by variants of the same strain of organism, such as *Clostridium botulinum,* are very similar in sequence with only minor differences in primary structure. In addition, applicant has specified certain leucine based motifs in claims 65 and 68 to 70.

Therefore, applicant submits that, in light of the specification and what is known in the art, the structure of the DNA itself is sufficiently described to make clear that

applicant was in possession of the invention as claimed at the time of filing the above-identified application, thereby complying with the written description requirement.

Currently pending claims 67 and 71 relate to a toxin which is recombinantly produced. Applicant submits that the specification, in view of, or together with, what is well known and understood by a molecular biologist of ordinary skill, provides for a description of producing the toxins of claims 65 and 71 recombinantly. For example, the specification on page 26, line 14 to page 27, line 2, discloses production of toxins of the present invention by recombinant DNA technology. In addition, "cook book" methods for producing recombinant proteins have been published and are available from a variety of sources. For example, Sambrook et al (Molecular Cloning, A Laboratory Manual, second edition, Cold Spring Harbor Press: 1989) is a well known, three volume, molecular cloning manual and provides detailed descriptions for cloning genes and expressing the protein product of the cloned genes. In view of the above, applicant submits that the written description requirement is fulfilled for the recombinant production of the claimed proteins.

In summary, applicant submits that the above-identified application includes a written description of the claimed invention sufficient to satisfy the requirements of 35 USC 112, first paragraph.

The Examiner rejects the claims under 35 USC 112, first paragraph, stating that the specification does not provide enablement for any uncharacterized structural modification. The Examiner also states that the specification is enabling for specific modified botulinum toxin type A proteins with a definable sequence change and a definable and assayable function.

Applicant traverses the rejection.

Currently pending, independent claim 65 calls for the deletion of the leucine based motif of SEQ ID NO 2 from botulinum toxin type A and recites that "the deletion decreases a half-life of the botulinum toxin type A." The leucine based motif of SEQ ID NO 2 is present in the carboxy terminal end of the light chain of botulinum toxin type A as can be seen in the well known amino acid sequence of botulinum toxin type A (see, for example, Binz et al supra and Minton supra).

Independent claim 68 calls for the addition of a leucine based motif, specified by SEQ ID NO 2, to a botulinum toxin type A. This claim recites that the addition of the leucine based motif increases a half-life of the botulinum toxin type A.

Applicant submits that this claim, and in particular, the above-identified recitation, is sufficiently enabled by the present disclosure. For example, it is well within the ability of a practitioner of ordinary skill in the fields of molecular biology to produce libraries of botulinum toxin type A proteins with a randomly added leucine based motif and to screen the libraries for active proteins produced with an increased half-life. This is a straightforward protocol which uses an already cloned and well defined gene sequence (botulinum toxin A gene sequence) and a simple seven amino acid sequence random mutation addition.

The Examiner previously cited Rudinger in the communication mailed December 31 2002, stating that the significance of a particular amino acid sequence for different aspects of biological activity cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. The protocol described in the previous paragraph is not similar to that of issue in Rudinger. For example, carrying out the procedure to identify the toxins with an increased half-life can be accomplished by routine experimentation by a technician of ordinary skill in the field.

Applicant submits that that the present claims clearly do not relate to "uncharacterized" structural modifications. To the contrary, the present claims relate to specifically defined proteins.

In summary, applicant submits that the present claims are sufficiently enabled to satisfy the requirements of 35 USC 112, first paragraph.

The Examiner rejects the claims under 35 USC 112, second paragraph, stating that the claims are indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, the Examiner states that the metes and bounds of a "structural modification" and to "alter" a biological persistence are not included in the claims.

Applicant traverses this rejection. However, currently pending claims 65 to 71 do not include the terms "structural modification" or "alter". Therefore, applicant submits that the present rejection should be withdrawn.

The Examiner rejects the claims under 35 USC 102(b) stating that the claims are anticipated by Johnson et al (US Patent No. 5,939,070).

Applicant traverses this rejection.

With regard to pending claims 65 to 71, Johnson et al does not disclose, teach or even suggest the present invention. For example, Johnson et al does not disclose, teach or even suggest the addition or deletion of a SEQ ID NO: 2 in a botulinum toxin, as recited in the present claims. In addition, Johnson et al does not disclose, teach or even suggest the addition or deletion of a SEQ ID NO: 2 in a botulinum toxin wherein the addition or deletion increases or decreases a half-life of the botulinum toxin type A, as recited in the present claims.

Therefore, applicant submits that the present claims are not anticipated by and are unobvious from and patentable over Johnson et al under 35 USC 102(b) and 103.

In conclusion, applicant has shown that presently pending claims 66 to 71 satisfy the requirements of 35 USC 112, first paragraph, and 35 USC 112, second paragraph; and are not anticipated by and are unobvious from and patentable over the prior art under 35 USC 102(b) and 103. Therefore, applicant submits that the present claims are allowable and respectfully requests that the above-identified application be issued at an early date.

Respectfully submitted,

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